REMARKS

Claims 16, 17, 21 – 26 are under examination. In the present response, reference to the specification is made using the paragraph numbers of published US Patent Application 2006/0147458 (SN 10/547,207).

1. Notice of Co-Pending Applications

Applicants respectfully request that the Examiner take note of the following co-pending patent applications, which are co-owned with the instant application:

Serial No.	Attorney Docket No.	Filing date
11/555,793	PG3886	2 Nov 06
10/515,871	PG4751	22 March 06
10/515,872	PG4852	2 Aug 05
10/571,972	VB60051	15 Mar 06

2. Claim amendments

Independent claim 17 has been amended to recite treatment of a MUC-1 over-expressing epithelial cell tumor in a mammal. This amendment is supported by the specification as filed, e.g. at paragraphs 0007 and 0008.

3. Enablement rejection: A prima facie case has not been made.

Claims 16, 17 and 21-26 stand rejected as non-enabled. Applicants assert that a prima facie case of non-enablement has not been made and request withdrawal of the rejection.

As discussed in MPEP 2164, in an enablement rejection "it is incumbent upon the Patent Office ... to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). According to In

re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. As stated in MPEP 2164.04 (underlining added):

> This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. ....References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

The Office Action states that "if the claimed nucleic acid were to be used in gene therapy, those of skill in the art would recognize the unpredictability of treating a disease by a method of gene therapy." (OA, page 3, para 9). However, all questions of enablement are evaluated against the claimed subject matter. Independent claim 17 recites a method of treating a MUC-1 over-expressing tumour in a mammal, by administering to the mammal a nucleic acid molecule encoding a MUC-1 protein to raise an immune response to MUC-1 in vivo. In contrast the Examiner's evidence and technical reasons are directed to the very broad field of "gene therapy" to treat any disease. The Office Action cites several references published more than five years before the present priority date, each of which deal broadly with gene therapy. No distinction is made in the Examiner's arguments between gene therapy to permanently replace a defective copy of a gene in a target tissue, and administration of nucleic acids to induce an immune response to the encoded protein. The Examiner has not provided technical reasons or evidence sufficient to establish that the present claims, directed to anti-cancer immunotherapy, are not enabled.

The present claims recite immunotherapy for the treatment of MUC1 overexpressing tumors. Applicants submit that adequate reasoning has not been provided to establish a non-enablement rejection of the present claims, and thus a prima facie case has not been made.

(a) The term "Gene therapy" encompasses approaches with distinct technical issues

The Examiner states that those of skill in the art recognize the unpredictability of treating "a disorder" by "gene therapy". In support, the Examiner cites Verma et al. (1997 Nature), Marshall (1995, Science) and Eck et al., (Goodman and Gilman, 9th edition, 1996) – all of which were published more than five years before the priority date (February 2003) of the present application.

Independent claim 17 recites a method of treating a MUC-1 over-expressing tumour in a mammal, by administering to the mammal a nucleic acid molecule encoding a MUC-1 protein to raise an immune response to MUC-1 in vivo. Thus, issues that are not pertinent to methods that raises an immune response to the expressed polypeptide, are not pertinent to the present claims.

Many 'gene therapies' are directed to inherited diseases "wherein a defective gene leads to the failure to synthesize a particular protein or to the synthesis of an abnormal protein. In either event, the absence of the normal protein can lead to a variety of clinical manifestations...." (Eck, page 77, first column, underlining added). In such cases, the goal of delivering nucleic acids to the subject is to provide a normal copy of the defective gene. As noted by Eck, "(a)lthough the defective gene is present in all cells of an individual with an inherited disorder, only a few tissues or organs actually express the gene and therefore are affected." In many cases, the nucleic acid must be delivered and function in a specific tissue (e.g., as in cystic fibrosis).

As further stated by Eck, 'gene therapies' may also be directed to treating "acquired diseases, such as AIDS, malignancies, and cardiovascular disease". (Eck, p. 78, first col., final para.) Eck notes that gene therapy to treat acquired disorders "has proceeded faster than applications for [inherited] single-gene defects for several reasons", including the fact that such applications may not require the long-term gene expression (months to years) needed to treat lifelong inherited diseases. Eck states that such long-term expression "has been difficult to achieve." (Eck, page 78, col. 1 final para to col. 2).

At page 81, Eck states that "gene therapy for neoplastic diseases includes efforts to engineer an immune response to tumor cells." The present claims are directed to achieving an immune response to an antigen expressed on tumor cells. Thus the 'gene therapy' issues which may be relevant to the present claims are those which pertain to nucleic acid vaccination to raise an immune response against an antigen that is overexpressed on a solid tumor. See paragraph 0063 of the specification (stating that the polynucleotides of the invention "may therefore be involved in recombinant protein synthesis, [or] utilised in DNA vaccination techniques.")

(b) Verma et al. (Nature 1997)

Like the Eck reference, Verma et al. (Nature, 1997) also notes the distinction between treating inherited diseases and treating acquired diseases such as cancer (see Table 1, page 240). Verma et al. identify three issues with 'gene therapy': lack of efficient delivery systems, lack of sustained expression, and undesirable host immune reactions (Verma, page 239, col. 1, end of first paragraph). Applicants submit, however, that these points do not support an enablement rejection of the present claims.

Verma discusses that DNA must be delivered to the correct target cell and, using the example of cystic fibrosis (an inherited disease), states that "it is still not clear that delivery of a correcting gene by this method will reach the right type of cell" (page 239, col 1, final para.). In contrast, the present claims are directed to administration of DNA encoding a tumor-associated immunogen to raise an immune response. At the time the present application was filed it was shown in the art that administration of DNA to the skin and muscle could raise potent immune responses, including immune reponses to model tumor antigens. See, e.g., Tuting et al., Current Opinions in Molecular Therapeutics 1:216 (1999; "The expression of a foreign protein in the skin or muscle following direct in vivo gene transfer results in the induction of potent cellular and humoral immune responses", Abstract); Dileo et al., Human Gene Therapy 14:79 (Jan 2003); Han et al., J. Virology 74:9712 (Oct. 2000); Tuting et al., Cancer Gene Therapy 6:73 (1999; "In summary, our studies

support the efficacy of plasmid-based immunization in two clinically relevant tumor model systems." (final paragraph)).

Verma et al. discusses issues related to viral vectors; because the present claims do not recite the use of viral vectors to the exclusion of DNA vaccination techniques, applicants submit that issues regarding viral vectors are not pertinent to the current enablement enquiry. The present specification discusses intradermal administration of DNA to induce an immune response. See e.g., specification paragraphs 0064 – 0072.

Verma et al. discuss lack of sustained expression in the context of treating life-long genetic illnesses, such as adenosine deaminase deficiency (ADA, see page 242, column 1 – 2). Applicants submit that this factor is not pertinent to the present enablement inquiry.

Verma et al. also discuss deleterious host immune responses to viral vectors (see e.g., page 239, col. 3, final paragraph; pages 240-241; page 242, columns 2-3). Applicants submit that this is not pertinent to enablement of the present claims, which do not recite viral vectors and where a specific immune response is desired.

The Office Action (paragraph 12) further cites Verma as teaching "in reference to ex vivo methods, that weak promoters produce only low levels of therapeutically effective protein", and that the search for effecitve enhancer-promoter combinations is "a case of trial and error for a given cell type" (citing Verma et al., p. 240, columns 2-3). However, the present claims do not recite an ex vivo method of gene therapy as defined by Verma (see page 240, top of column 2, ex vivo gene therapy described as removing target cells from the subject, infecting the target cells with a therapeutic recombinant retroviral vector, and transplanting the cells back into the subject). Applicants submit that this discussion does not present a specific technical reason to doubt the enablement of the present claims.

(c) Marshall et al., (Science, 1995)

Marshall (1995) is cited by the Office Action as stating that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-

remain a nagging problem for the entire field" and that "many problems must be solved before gene therapy will be useful for more than the rare application" (p. 1054, col. 3, para 2 and p. 1055, col. 1). This article is primarily directed to therapies to treat genetic disorders such as cystic fibrosis (CF) and ADA deficiency. Applicants respectfully request that the Examiner clarify where Marshall et al. provides evidence that supports specific findings of fact that establish the present claims are not enabled.

(d) Eck et al. (Goodman & Gilman, 1996)

The Office Action quotes Eck et al. (1996): "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today." The Office Action further cites Eck as teaching that:

> (W)ith in vivo gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.,), the in vivo consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced.

The Office Action notes that "these factors differ dramatically based on the vector used, the protein being produced and the disease being treated." (citing Eck et al., bridging pages 81-82).

However, the Office Action does not explain how these general issues apply to the present claims to establish a prima facie lack of enablement. As stated in MPEP 2164.04, specific findings of fact, and specific technical reasons must be supplied to support a prima facie lack of enablement. The enablement inquiry must be directed to the claimed subject matter.

4. Enablement: How to make and use

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue

experimentation' (see e.g. In Re Wright, 990 F.2d 1557, 1561). However, the Examiner has not clearly stated whether the current enablement rejection is based on the 'making' or 'using' of the claimed invention.

While Applicants believe that no question has been raised regarding the ability of one skilled in the art to make the nucleotide constructs, Applicants request clarification on whether the Examiner maintains that one of ordinary skill in the art (a) could not make the constructs used in the claimed methods, or (b) could not use the claimed method to induce an anti-MUC1 immune response in a mammal by administering the described nucleotide constructs.

The present enablement rejection appears to rest on the assertion that one of skill in the art could not achieve therapeutic "success" without undue experimentation. The Office Action makes the conclusory statement that "gene therapy" using recombinant nucleic acids "has not seen any success despite a great deal of work and resources" (paragraph 10), and that "no correlation exists between successful expression of a gene and a therapeutic result" (citing Ross et al. (1996)). Verma refers to the more than 200 clinical trials underway as of the time the article was published (1997) to conclude that "there is still no single outcome that we can point to as a success story" (page 239, second paragraph).

Applicants request the Examiner to clarify what is meant by success. If the Examiner believes clinical success must be shown, Applicants maintain that this is not a correct standard.

The difference between legal standards of patentability and clinical success of an invention was addressed in In re Brana:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought.

(34 USPQ2d 1436 (Fed. Cir. 1995)). The court continued, stating "The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption."

In CFMT Inc. V. Yieldup Int'l Corp. , 349 F.3d 1333, 1338; 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) stated that "(e)nablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." Applicants submit that likewise, enablement of a medical method does not require that the method meet the same standards for introduction of a new method into clinical practice.

Further, In re Brana at 1442, states "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."

Applicants further submit that the articles discussed above (Tuting et al. (Human Gene Ther. 2003), Tuting et al., (Cancer Gene Therapy 1999); Dileo et al. (Human Gene Ther. 2003); and Han et al. (J. Virology 2000)) are evidence of enablement of the current claims.

5. Clarification requested

The Examiner concludes that "the art clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low. Thus the claimed method of treatment ... would not have substantial utility without undue experimentation" (Office Action, paragraph 13, underlining added). Applicants request clarification whether the Examiner is also making a lack of utility rejection under 35 USC section 101.

6. Conclusion

Applicants maintain that a prima facie case of non-enablement of the claimed method has not been made. Reference to general issues regarding viral vector gene therapies to treat disease by establishing long-term expression of a protein in

a particular target tissue do not provide the required specific findings of fact, supported by evidence, to conclude that the present claims are non-enabled.

At the time the present application was filed it was shown in the art that administration of DNA to the skin and muscle could raise potent immune responses, including immune reponses to model tumor antigens. See, e.g., Tuting et al., Current Opinions in Molecular Therapeutics 1:216 (1999; "The expression of a foreign protein in the skin or muscle following direct in vivo gene transfer results in the induction of potent cellular and humoral immune responses", Abstract); Dileo et al., Human Gene Therapy 14:79 (Jan 2003); Han et al., J. Virology 74:9712 (Oct. 2000); Tuting et al., Cancer Gene Therapy 6:73 (1999; "In summary, our studies support the efficacy of plasmid-based immunization in two clinically relevant tumor model systems." (final paragraph)). Applicants submit that the present claims are enabled; withdrawal of the present rejection is requested.

Respectfully submitted,

Dated:11 August 2008

/Virginia G. Campen/
Virginia G. Campen
Attorney for Applicant
Reg. No. 37,092
Tel. (919) 483-1012
Fax. (919) 483-7988